Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Solid Tumour Section

Mini Review

Soft tissue tumors: Clear cell sarcoma

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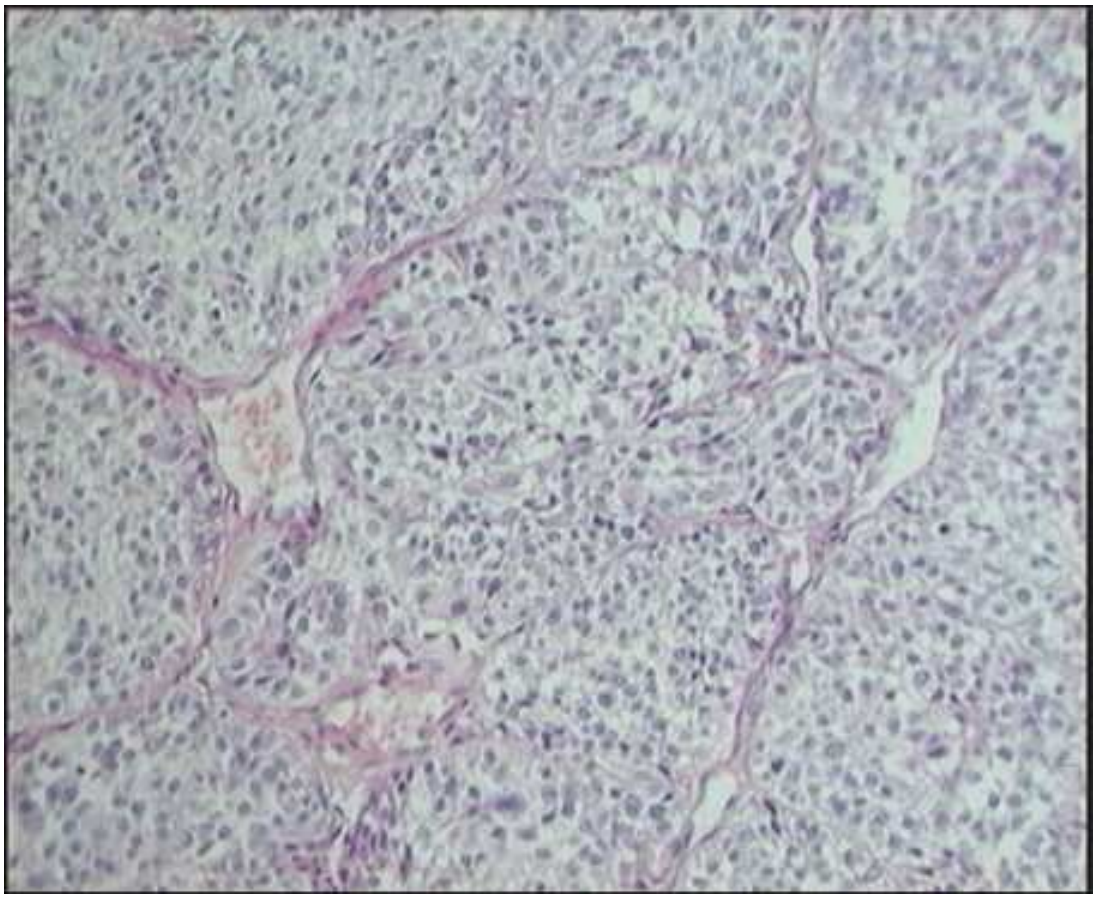
Published in Atlas Database: November 2002

Online updated version : http://AtlasGeneticsOncology.org/Tumors/ClearCellSarcID5074.html
DOI: 10.4267/2042/37939

Identity

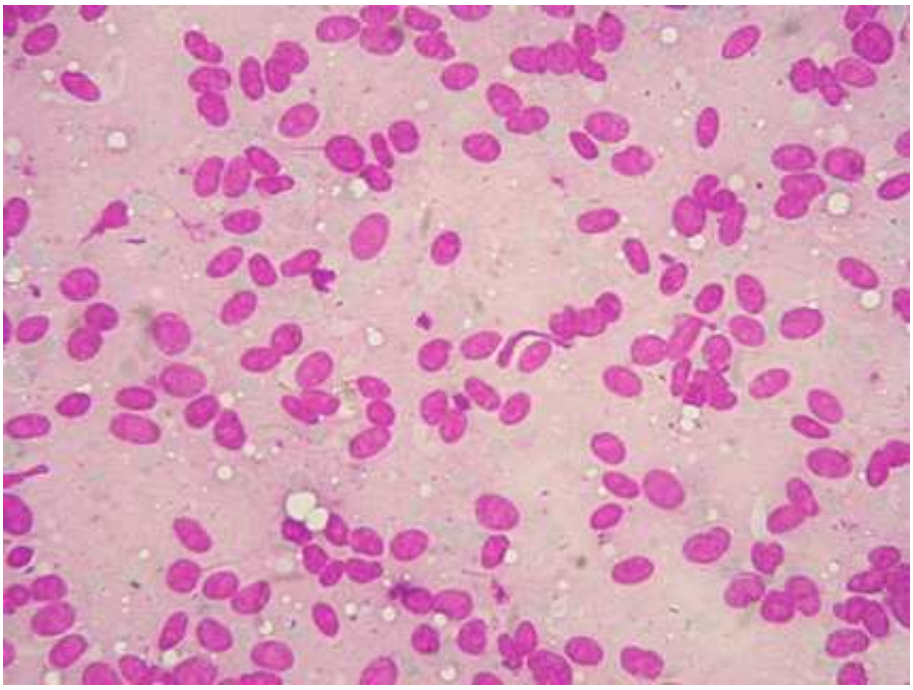
Alias

Clear cell sarcoma of the tendons and aponeuroses
Malignant melanoma of the soft parts



Nests of clear polygonal cells delineated by fibrous septa (HE, 200x).

Clinics and pathology



Cellular smear almost exclusively showing dispersed spindle cells. Their oval nuclei are only slightly irregular and contain a large nucleolus. The cytoplasm is rather scant (MGG, 400x) (Courtesy of Dr. J. Willems, Onze-Lieve-Vrouw Ziekenhuis Aalst, Belgium).

Disease

Soft tissue tumour, presenting as a slow growing mass intimately associated with tendons and aponeuroses, in young adults.

Note

To be distinguished from clear cell sarcoma of the kidney, to which it is unrelated.

Embryonic origin

Mesoderm.

Epidemiology

Rare sarcoma affecting primarily young adults

Clinics

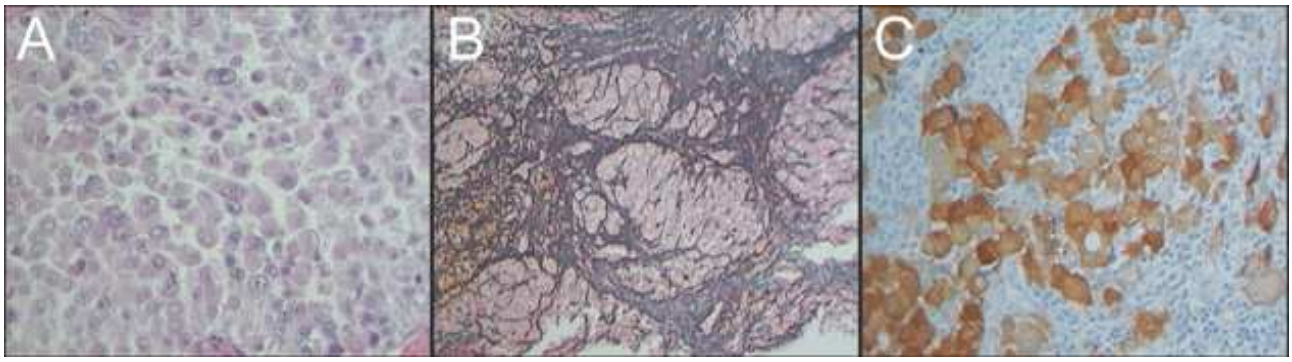
Slowly growing tumour mass, causing pain or tenderness, particularly frequently (up to 95% of the cases) situated in the extremities, with a predilection for the foot and the ankle.

Pathology

Polygonal or spindle shaped cells with abundant eosinophilic or clear cytoplasm displaying a uniform, nested to fascicular growth pattern, delineated by fibrous septa. Melanin deposits can be demonstrated using specific stains, but is more readily detectable by immunoreactivity against melanoma antigens (e.g. S100 and HMB45) in the vast majority of the cases.

Treatment

Radical surgical resection, adjuvant radiotherapy should be considered in incomplete resections, large (>5 cm) tumours and/or high grade lesions. Clear cell sarcomas seem to display little sensitivity to conventional soft tissue sarcoma multi-agent chemotherapy protocols.



Left to right: A: Typical clear cell sarcoma with eosinophilic cytoplasm (H&E, 400x); B: A reticulin meshwork surrounds the individual nests (reticulin, 200x); C: Strong S100 immunoreactivity, a consistent feature (S100, 400x).

Evolution

Special attention should be paid to the occurrence of late recurrences (median time to recurrence: 4.2 years).

Prognosis

Generally, clear cell sarcoma is characterised by an adverse prognosis, only 40 to 50% of the patients being long-term survivors. As recurrences may occur late, 5-year survival rates tend to misjudge prognosis. Established prognostic features include: tumour size, necrosis and local recurrence.

Cytogenetics

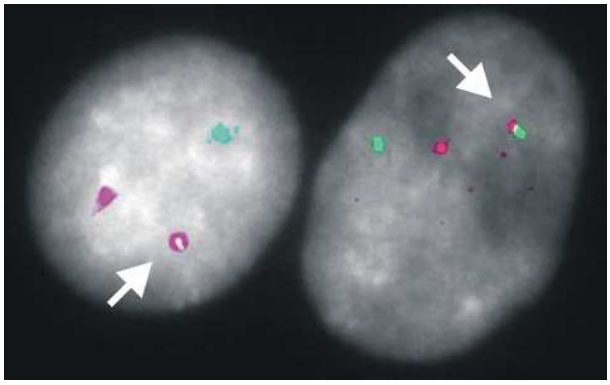
The t(12;22)(q13;q12), as identified by G-banding.

Cytogenetics Morphological

The cytogenetic hallmark of clear cell sarcoma is the presence of the t(12;22)(q13;q12). This translocation has been described in the majority of reported clear cell sarcoma cases, not however in other malignancies. The translocation is readily identifiable with G-, R- or Q-banding.

Cytogenetics Molecular

Fluorescence in situ hybridisation based approaches can be used to demonstrate the t(12;22), using chromosome painting probes or to demonstrate EWSR1 and ATF1 gene rearrangement, using gene specific probes.



Dual colour in situ hybridisation the EWS cosmid G9 (green) and the ATF1 CCS2.2 cosmid (red) demonstrating a juxtaposition of 5' EWS to 3' ATF1 sequences, indicating the presence of a EWS/ATF1 genomic fusion (arrowheads).

Probes

EWSR1 probes: 5' EWSR1: G9 cosmid; 3' ATF1 probe: CCS2.2

Additional anomalies

Although the t(12;22) has been reported as the sole chromosomal aberration in clear cell sarcoma, most cases display additional cytogenetic anomalies, including +7, +8 and structural and numerical aberrations of chromosome 22.

Variants

No variant translocations, creating EWSR1/ATF1 fusion transcripts, have been described.

Genes involved and proteins

EWSR1

Location
22q13

Note
Also called EWS.

DNA / RNA

EWSR1 is transcribed from centromere to telomere at 22q12. The coding sequence contains 1971 bp, comprising 17 exons and spans approximately 32 kb. Alternative splicing creates the EWS-b variant, lacking exons 8 and 9.

Protein

The EWS protein contains a C-terminal RNA binding domain and has indeed been shown to display RNA binding properties. The functions of the EWS protein, however, largely remain elusive.

ATF1

Location

12q13

DNA / RNA

ATF1 is transcribed from centromere to telomere at 12q13. The coding sequence contains 816 bp, comprising 6 exons and spans approximately 43 kb.

Protein

ATF1 encodes a member of the CREB/ATF basic leucine-zipper type transcription factor family and binds to cAMP inducible promotors.

Result of the chromosomal anomaly

Hybrid Gene

Description

The EWS/ATF1 fusion transcript is detectable in up to 90% of the clear cell sarcoma cases. As described in other EWS rearrangements, the transcript fuses 5' EWS to 3' heterologous sequences. The reciprocal ATF1/EWS fusion probably does not contribute to malignant transformation since it is out of frame.

Transcript

Several alternatively spliced transcripts have been described, the more frequent being the type 1 fusion: EWS exon 8 fused to ATF1 exon 4.

Fusion Protein

Oncogenesis

The EWS/ATF1 oncoprotein converts ATF1 to a constitutive transcriptional activator that represses p53/CBP-mediated transactivation.

Primer pair	Primer name	Primer sequence	TA (°C)*	Product size
EWS-ATF1 Type 1 or 2 outer pair	EWSex8-F1	GAGGCATGAGCAGAGGTGG	58°	Type 1 : 246 bp
	ATF1-R1	GAAGTCCCTGTACTCCATCTGTG		Type 2 : 183 bp
EWS-ATF1 Type 1 or 2 inner pair	EWSex8-F2	GAGGAGGACGCGGTGGAATG	64°	Type 1 : 185 bp
	ATF1-R2	CTGTAAGGCTCCATTTGGGGC		Type 2 : 122 bp
EWS-ATF1 Type 3 outer pair	EWSex7-F1	TCCTACAGCCAAGCTCCAAGTC	58°	Type 3 : 124 bp
	ATF1-R1	See above		
EWS-ATF1 Type 3 inner pair	EWSex7-F2	TATAGCCAACAGAGCAGCAG	55°	Type 3 : 63 bp
	ATF1-R2	See above		

Detection protocole: as described by Antonescu et al. (the data given are virtually identical to the Table 1 from the mentioned reference).

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This article should be referenced as such:

Poppe B, Forsyth R, Dhaene K, Speleman F. Soft tissue tumors: Clear cell sarcoma. Atlas Genet Cytogenet Oncol Haematol. 2003; 7(1):49-53.